

Predicting QT interval prolongation in patients diagnosed with the 2019 novel coronavirus infection

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Abstract

Introduction: 2019 novel coronavirus (COVID-19) patients frequently develop QT interval prolongation that predisposes them to Torsades de Pointes and sudden cardiac death. Continuous cardiac monitoring has been recommended for any COVID-19 patient with a Tisdale Score of seven or more. This recommendation, however, has not been validated.

Methods: We included 178 COVID-19 patients admitted to a non-intensive care unit setting of a tertiary academic medical center. A receiver operating characteristics curve was plotted to determine the accuracy of the Tisdale Score to predict QT interval prolongation. Multivariable analysis was performed to identify additional predictors.

Results: The area under the curve of the Tisdale Score was 0.60 (CI 95%, 0.46–0.75). Using the cutoff of seven to stratify COVID-19, patients had a sensitivity of 85.7% and a specificity of 7.6%. Risk factors independently associated with QT interval prolongation included a history of end-stage renal disease (ESRD) (OR, 6.42; CI 95%, 1.28–32.13), QTc \geq 450 ms on admission (OR, 5.90; CI 95%, 1.62–21.50), and serum potassium \leq 3.5 mmol/L during hospitalization (OR, 4.97; CI 95%, 1.51–16.36).

Conclusion: The Tisdale Score is not a useful tool to stratify hospitalized non-critical COVID-19 patients based on their risks of developing QT interval prolongation. Clinicians should initiate continuous cardiac monitoring for patients who present with a history of ESRD, QTc \geq 450 ms on admission or serum potassium \leq 3.5 mmol/L.

KEYWORDS

continuous cardiac monitoring, COVID-19, end-stage renal disease, hypokalemia, QT interval prolongation, Tisdale Score

1 | INTRODUCTION

The 2019 novel coronavirus (COVID-19) is increasingly recognized as a multi-organ infectious disease that goes far beyond the respiratory system. One of its common complications involves cardiac injuries in patients even without underlying heart conditions (Driggin et al., 2020). This cardiac involvement can manifest as asymptomatic

troponin elevation to catastrophic cardiac arrhythmia (Driggin et al., 2020). In one study, arrhythmia was observed in 44.4% of COVID-19 patients admitted to the intensive care unit (ICU) and 6.9% of those managed on general wards (Wang et al., 2020a). The increased risk of arrhythmia in COVID-19 patients can be explained by metabolic stress, a hypercoagulable state, direct myocardiocyte infection and cytokine storm (Lazzerini et al., 2020). We are interested in

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identifying the subset of COVID-19 patients at high risk of developing QT interval prolongation during hospitalization. QT interval prolongation can deteriorate into Torsades de Pointes (TdP) and lead to sudden cardiac death (Yap & Camm, 2003). In addition, it is also one of the few rhythm abnormalities that, if recognized early, can potentially be prevented. An observational study from multiple hospitals in New York found that 6.1% of COVID-19 patients presented with QT intervals greater than 500 ms on admission (Richardson et al., 2020). In comparison, the incidence of QT intervals greater than 500 ms in the general population is less than one percent (Mizusawa & Wilde, 2013). The higher risk of QT interval prolongation among COVID-19 patients is further complicated by the widespread use of QT-prolonging medications, including hydroxychloroquine and azithromycin (Chorin et al., 2020a; Mercurio et al., 2020), despite their ineffectiveness (Chen et al., 2020; Geleris et al., 2020; Wang et al., 2020b). Therefore, identifying patients at high risk for QT interval prolongation is a critical step in managing COVID-19 patients.

In 2013, Tisdale et al reported a risk model to predict QT interval prolongation in critically ill patients admitted to the cardiac critical care unit (Tisdale et al., 2013). It incorporates nine variables and stratifies patients into low-, medium- or high-risk groups depending on their cumulative scores. Experts suggest that a Tisdale Score of seven or more in COVID-19 patients indicates the need for continuous cardiac monitoring of catastrophic cardiac events (Simpson et al., 2020). Generalization of the performance of the Tisdale Score in a critically ill population with severe underlying heart conditions to COVID-19 patients, however, may overestimate the risk of QT interval prolongation. Therefore, the performance of the Tisdale Score remains to be evaluated in hospitalized COVID-19 patients. In addition to the Tisdale Score, other potential risk factors should be evaluated to determine their usefulness in stratifying hospitalized COVID-19 patients based on their risks of developing QT interval prolongation.

Our study aims to answer a question that every clinician faces in the middle of COVID-19 pandemic: which COVID-19 patients will benefit from continuous cardiac monitoring and what we can offer to minimize the risk of QT interval prolongation? We focused on the non-critical patients for whom decisions on initiating continuous cardiac monitoring need to be made. Reliably identifying COVID-19 patients who will or will not benefit from continuous cardiac monitoring should help achieve better patient care and prioritize medical resources.

2 | METHODS

2.1 | Study design

We conducted a single-center retrospective study evaluating adults with confirmed COVID-19 infection by nasopharyngeal reverse transcriptase-polymerase chain reaction (RT-PCR) who were admitted to a non-ICU setting of Ascension St. John Hospital, Detroit, Michigan from March 1, 2020, to April 30, 2020. This study was approved by Ascension St. John Hospital Institutional Review Board. Inclusion criteria were confirmed COVID-19 infection, the corrected QT interval (QTc) less than 500 ms on admission, at least one follow-up electrocardiogram (EKG) during hospitalization, and admission to a non-ICU setting. Exclusion criteria were QTc equal or more than 500 ms on admission, no follow-up EKG, discharge from emergency room, or admission to ICU. Electronic medical records were reviewed to collect demographic and clinical data, including age, sex, race, comorbidities, medications received during the hospitalization, laboratory results and serial EKGs. The Tisdale Score was retrospectively calculated for each included patient. The standard regimen of azithromycin, if used, was 500 mg daily on day one followed by 250 mg daily on days two to five. The standard regimen of hydroxychloroquine, if used, was 400 mg twice daily on day one followed by 200 mg twice daily on days two to five. QT-prolonging medications were further classified into low risk, moderate risk or high risk according to their potential to cause QT interval prolongation (Table 1). Each 12-lead EKG was reviewed by at least one investigator (WZ, NG, and SA). QT interval was determined using the tangent method in lead II or alternatively V5-V6 if the T wave was not easily identified in lead II. QT interval was corrected for heart rate using the Bazett formula: $QTc = QT/\sqrt{RR}$. If a patient had a paced rhythm or an underlying left bundle branch block, we used the following formula to calculate QTc: $QTc = (QT - [0.7 \times QRS - 50]) / \sqrt{RR}$ (Wang et al., 2015). Our outcome of interest was newly developed QT interval prolongation during hospitalization, defined as a corrected QTc ≥ 500 ms or an increase in QTc ≥ 60 ms compared with the baseline QTc.

2.2 | Statistical analysis

Descriptive statistics were calculated to characterize the study groups. Continuous variables were described as the mean with

Risk Stratification	Medications
High risk	Procainamide, amiodarone, sotalol, propafenone, haloperidol IV
Moderate risk	Azithromycin, fluconazole, voriconazole, levofloxacin, moxifloxacin, gemifloxacin, pentamidine, ondansetron, haloperidol PO, olanzapine, quetiapine, risperidone, SSRIs, TCAs
Low risk	Hydroxychloroquine, metoclopramide, hydroxyzine, donepezil, trazodone, hydrocodone, methadone, buprenorphine

TABLE 1 Classification of QT-prolonging medications based on their risks of causing QT interval prolongation

Abbreviations: IV, intravenous; PO, per os; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

standard deviation (SD) or the median with interquartile range (IQR). Categorical variables were described as frequency distributions. Receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was used to assess the ability of the Tisdale Score to predict the outcome of interest. Sensitivity and specificity were computed based on different cutoffs of the Tisdale Score. Univariable analysis was done using Student's *t* test, the chi-squared test, and the Mann-Whitney *U* test. Variables with a *p*-value less than 0.05 were selected to enter a multivariable logistic regression model using backward likelihood ratio test (LRT) algorithm. All data were analyzed using SPSS (v 27.0) and R (version 4.00). A *p*-value less than .05 was considered to indicate statistical significance.

3 | RESULTS

We included 178 non-critical COVID-19 patients who were admitted to a non-ICU setting following laboratory confirmation of their COVID-19 status (Table 2). The mean (SD) age was 63.5 (15.4) years; 93/178 (52.2%) of our cohort were male. The majority of patients, 139/178 (78.1%) were black. Among the pre-existing conditions that have been associated with prolonged QT interval (Lehmann & Morady, 2003; Malik et al., 2017; Tsiompanidis et al., 2018), congestive heart failure with reduced ejection fraction (HFrEF), coronary artery disease (CAD), chronic liver disease, chronic kidney disease (CKD), and end-stage renal disease (ESRD) were present in 11/178 (6.2%), 23/178 (12.9%), 7/178 (3.9%), 32/178 (18.0%), and 11/178 (6.2%) patients, respectively. For the antiviral regimen, 134/178 (75.3%) patients received azithromycin and 155/178 (87.1%) received hydroxychloroquine. The mean (SD) number of QT-prolonging medications used for each patient was 2.3 (1.0). 117/178 (65.7%) patients had 2 EKGs, 38/178 (21.3%) had 3 EKGs, 13/178 (7.3%) had 4 EKGs, and 10/178 (5.6%) had more than 4 EKGs. The mean (SD) baseline QTc calculated from the first EKG obtained on admission was 447.2 (25.9) ms. The mean (SD) peak QTc calculated from serial EKGs during hospitalization was 463.3 (30.3) ms. The incidence of QT interval prolongation was 11.8% (21/178). The median (IQR) length of stay was 6.2 (4.0–10.3) days. The case fatality rate was 13.5% (24/178), caused by respiratory failure, multi-organ failure or cardiac arrest.

The Tisdale Score was retrospectively calculated for each patient. The mean (SD) Tisdale Score was 10.6 (2.8). The majority of patients, 163/178 (91.6%) had a Tisdale Score of seven or above. Using the Tisdale Score of seven as the cutoff yielded a sensitivity of 85.7% and a specificity of 7.6%. An ROC curve was plotted to evaluate the performance of the Tisdale Score to predict QT interval prolongation in hospitalized non-critical COVID-19 patients (Figure 1). The AUC of the Tisdale Score was 0.60 (CI 95%, 0.46–0.75). These results collectively showed that using the Tisdale Score was inadequate to identify the hospitalized non-critical COVID-19 patients who were at increased risk of developing QT interval prolongation.

To identify the predictors for QT interval prolongation in hospitalized non-critical COVID-19 patients, we performed univariable

TABLE 2 Baseline characteristics of 178 COVID-19 patients in the non-ICU setting

Characteristics	Value
Age, mean (SD), y	63.5 (15.4)
Sex, No. (%)	
Male	93 (52.2)
Female	85 (47.8)
Race, No. (%)	
Black	139 (78.1)
White	35 (19.7)
Other	4 (2.2)
Length of stay (d), median (IQR)	6.2 (4.0–10.3)
Severity, No. (%)	
Mild	2 (1.1)
Moderate	12 (6.7)
Severe	160 (89.9)
Critical	4 (2.2)
Mortality, No. (%)	24 (13.5)
Pre-existing conditions	
HFrEF, No. (%)	11 (6.2)
CAD, No. (%)	23 (12.9)
Chronic liver disease, No. (%)	7 (3.9)
CKD, No. (%)	32 (18.0)
ESRD, No. (%)	11 (6.2)
Laboratory values	
CRP on admission (mg/dl), median (IQR)	82.4 (37.3–143.0)
Potassium \leq 3.5 mmol/L during hospitalization, No. (%)	80 (44.9)
Complications	
Acute myocardial infarction on admission, No. (%)	0 (0)
Acute heart failure on admission, No. (%)	1 (0.6)
Sepsis on admission, No. (%)	136 (76.4)
AKI during hospitalization, No. (%)	64 (36.0)
Medications	
Loop diuretics, No. (%)	28 (15.7)
Azithromycin, No. (%)	134 (75.3)
Hydroxychloroquine, No. (%)	155 (87.1)
Number of QT-prolonging medications per patient, mean (SD)	2.3 (1.0)
EKG	
QTc interval on admission, mean (SD)	447.2 (25.9)
Peak QTc interval during hospitalization, mean (SD)	463.3 (30.3)
QT prolongation, No. (%)	21 (11.8)
Tisdale Score, mean (SD)	10.6 (2.8)

Abbreviations: AKI, acute kidney injury; CAD, coronary artery disease; CKD, chronic kidney disease; CRP, c-reactive protein; ESRD, end-stage renal disease; IQR, interquartile range; QTc, corrected QT interval; SD, standard deviation.

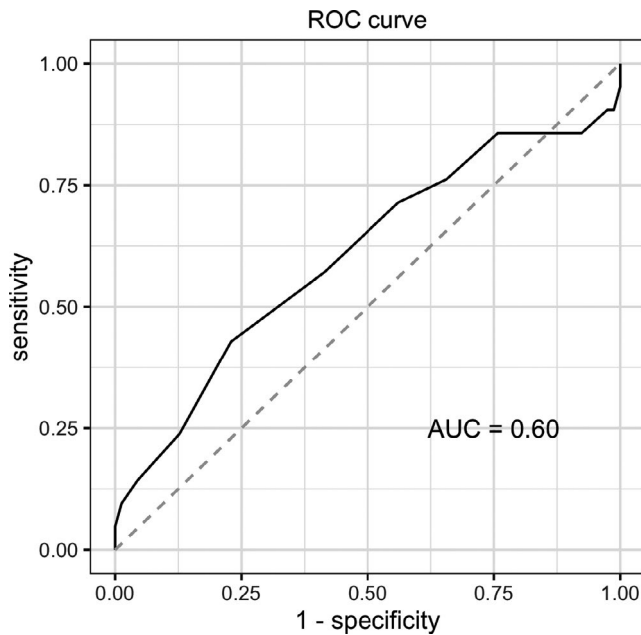


FIGURE 1 The Tisdale Score was not useful to predict QT interval prolongation in COVID-19 patients. The dotted line represents no discrimination capacity with AUC of 0.5. The solid line represents the Tisdale Score with AUC of 0.60. AUC, area under the curve; ROC, receiver operating characteristics

analysis (Table 3) followed by multivariable logistic regression (Figure 2) of potentially contributing variables. We found that a history of end-stage renal disease (ESRD) (OR, 6.42; CI 95%, 1.28–32.13), QTc \geq 450 ms on admission (OR, 5.90; CI 95%, 1.62–21.50), and serum potassium \leq 3.5 mmol/L during hospitalization (OR, 4.97; CI 95%, 1.51–16.36) were independently associated with QT interval prolongation in hospitalized non-critical COVID-19 patients. Of note, the use of azithromycin and hydroxychloroquine were not associated with increased risk of QT interval prolongation after controlling for other factors.

4 | DISCUSSION

The incidence of QT interval prolongation in COVID-19 patients who were admitted to a non-ICU setting of our hospital was 11.8%. In comparison, Tisdale et al reported approximately 30% incidence of QT interval prolongation in the patients who were admitted to the Cardiac Critical Care Units at the Indiana University Health Methodist Hospital (Tisdale et al., 2013). The discrepancy in the incidence of QT interval prolongation further proves that these two patient populations are very different. Generalization of the findings from Tisdale's study to COVID-19 patients will undoubtedly invite errors. Two major problems arise when clinicians use the Tisdale Score to predict COVID-19 patients' risks of developing QT prolongation during hospitalization. First, some items in the Tisdale Score do not apply to the vast majority of COVID-19 patients because the Tisdale Score was primarily designed for patients who presented with critical cardiac conditions. These items include

“Being admitted for acute myocardial infarction” and “Being admitted for heart failure.” Second, using the Tisdale Score of seven as the cutoff to predict QT interval prolongation in hospitalized non-critical COVID-19 patients has an adequate sensitivity of 85.7% but a poor specificity of 7.6%. Attempting to find the optimal cutoff of the Tisdale Score for hospitalized COVID-19 patients also yielded unsatisfactory results.

To help stratify the COVID-19 patients based on their risks of developing QT interval prolongation during hospitalization, potentially contributing variables were evaluated in our study. We found that the risk of developing QT interval prolongation was independently associated with a history of ESRD, QTc interval \geq 450 ms on admission and serum potassium \leq 3.5 mmol/L during hospitalization. Interestingly, COVID-19 patients with a history of ESRD are at risk of developing QT interval prolongation, whereas those who developed acute kidney injury (AKI) are not at risk. This finding supports that chronic cardiac ion channel remodeling induced by long-standing renal insufficiency rather than metabolic derangement predominantly contributes to cardiac repolarization abnormalities in hospitalized COVID-19 patients. A possible molecular mechanism involves a progressive reduction of the naturally redundant potassium channels and a concomitant increase in sensitivity of the remaining potassium channels to pharmaceutical inhibition (Gussak & Gussak, 2007). It is a worthwhile endeavor to investigate whether COVID-19 could further alter the number or function of cardiac ion channels in ESRD patients in the future. In line with our findings, we recommend that the hospitalized COVID-19 patients with any of these three risk factors who do not require intensive care be put on continuous cardiac monitoring and that every effort be made to keep serum potassium above 3.5 mmol/L.

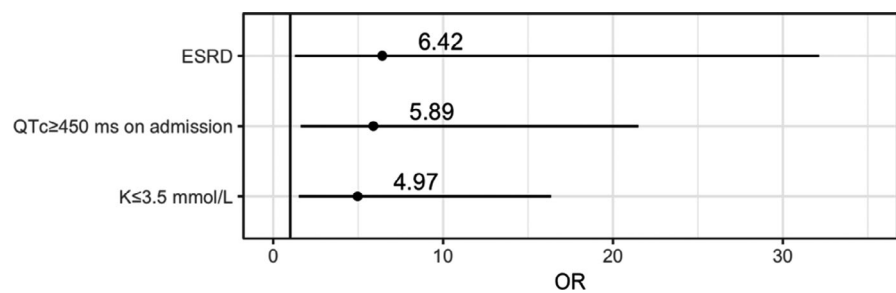
The etiologies that predispose COVID-19 patients to QT interval prolongation are multifactorial. cardiomyocyte infection, dysregulated systemic inflammatory states, sympathetic hyperactivation, pre-existing medical conditions, and current medications have been reported to collaboratively contribute to this process. This concept is further supported by our study that multiple factors are involved. Nevertheless, the use of hydroxychloroquine or azithromycin has been taking the most blame. One retrospective study showed that 21% of COVID-19 patients who received both hydroxychloroquine and azithromycin developed prolonged QTc exceeding 500 ms, and 13% of patients had an increase in QTc by more than 60 ms (Mercurio et al., 2020). Another retrospective study showed that the mean QTc increased from 443 ± 25 ms to a maximum of 473 ± 40 ms in COVID-19 patients who received both hydroxychloroquine and azithromycin (O'Connell et al., 2020). These studies, however, did not include COVID-19 patients who received none of these medications as a control group. As a result, the association between the use of hydroxychloroquine and azithromycin and the risk of developing QT interval prolongation in hospitalized COVID-19 patients was not established. Our cohort showed no association between the use of hydroxychloroquine and azithromycin and the risk of developing QT interval prolongation after controlling for other risk factors. This finding is consistent with the observation that azithromycin (Choi et al., 2018) and hydroxychloroquine (Chen et al., 2006) are an uncommon

TABLE 3 Univariable analysis of predictors for QT interval prolongation in COVID-19 patients

Variables	QT interval prolongation		OR (95% CI)	p-Value
	No (n = 157)	Yes (n = 21)		
Age, mean (SD)	63.6 (16.1)	62.9 (9.8)		.79
Sex, No. (%)				
Male	82 (52.2)	11 (52.4)	0.99 (0.40–2.47)	.99
Female	75 (47.8)	10 (47.6)		
Race, No. (%)				
Black	122 (77.7)	17 (80.9)		.59
White	32 (20.4)	3 (14.3)		
Other	3 (1.9)	1 (4.8)		
HFrEF, No. (%)	8 (5.1)	3 (14.3)	3.10 (0.76–12.77)	.10
CAD, No. (%)	19 (12.1)	4 (19.0)	1.71 (0.52–5.62)	.37
Chronic liver disease, No. (%)	5 (3.2)	2 (9.5)	3.2 (0.58–17.63)	.16
CKD, No. (%)	25 (15.9)	7 (33.3)	2.64 (0.97–7.20)	.05
ESRD, No. (%)	7 (4.5)	4 (19.0)	5.04 (1.34–19.01)	.009
QTc \geq 450 ms on admission, No. (%)	67 (42.7)	18 (85.7)	8.06 (2.28–28.49)	<.0001
CRP on admission, median (IQR)	80 (37.1–143.1)	96.2 (50.5–142.7)		.50
Potassium \leq 3.5 mmol/L, No. (%)	64 (40.8)	16 (76.2)	4.65 (1.62–13.33)	.002
Sepsis on admission, No. (%)	122 (77.7)	14 (66.7)	0.57 (0.22–1.53)	.26
AKI during hospitalization, No. (%)	56 (35.7)	8 (38.1)	1.11 (0.43–2.84)	.83
Loop diuretics, No. (%)	25 (15.9)	3 (14.3)	0.88 (0.24–3.21)	.85
Azithromycin, No. (%)	122 (77.7)	12 (57.1)	0.38 (0.15–0.98)	.04
Hydroxychloroquine, No. (%)	138 (87.9)	17 (81.0)	0.59 (0.18–1.92)	.37
QT-prolonging medications, No. (%)				
0	5 (3.2)	1 (4.8)		.35
1	20 (12.7)	5 (23.8)		
\geq 2	132 (84.1)	15 (71.4)		
High-risk QT-prolonging medications, No. (%)	4 (2.5)	3 (14.3)	6.38 (1.32–30.78)	.009

Abbreviations: AKI, acute kidney injury; CAD, coronary artery disease; CKD, chronic kidney disease; CRP, c-reactive protein; ESRD, end-stage renal disease; IQR, interquartile range; QTc, corrected QT interval; SD, standard deviation.

FIGURE 2 Predictors for QT interval prolongation in hospitalized non-critical COVID-19 patients. The values represent the mean estimated odds ratio of each predictor. The horizontal lines represent 95% CI. ESRD, end-stage renal disease; QTc, corrected QT interval



cause of QT prolongation. Instead of tunneling our vision to medications only, clinicians should consider multiple risk factors as a whole.

4.1 | Study limitations

We are aware of the limitation that our study has as a retrospective chart review of COVID-19 patients admitted to our hospital

from March 1, to April 30, 2020. Only 178 of 773 patients (23.0%) remained after the inclusion and exclusion criteria were applied. 21 of 178 patients (11.8%) developed QT interval prolongation during their hospitalization. Therefore, the number of patients available for statistical analysis may not be enough to uncover the statistical significance of some risk factors. One example is the number of high-risk QT-prolonging medications COVID-19 patients were taking. Seven of 178 (3.9%) patients received these medications. Our study

found no association between the number of high-risk QT-prolonging medications used during hospitalization and the risk of developing QT interval prolongation after controlling for other risk factors. Were there more patients enrolled in our study, its significance would be definitively determined. Consistent with our argument, the use of amiodarone, a high-risk QT-prolonging medication, has been reported to be associated with QT interval prolongation in COVID-19 patients (Chorin et al., 2020b). As a result, we believe that the number of high-risk QT-prolonging medications COVID-19 patients were taking is a clinically significant risk factor for QT interval prolongation that should not be overlooked. Clinicians need to balance the necessity of continuing or adding these medications with the risk of causing QT interval prolongation, particularly for patients who already have other risk factors. In addition, EKGs were not performed regularly and varied significantly between individual patients. Depending on their presenting QT interval, comorbidities and length of hospitalization, patients received between 2 and 14 EKGs at discretion of internists and cardiologists. As a result, transient QT prolongation episodes might be missed in some patients, and the incidence of QT prolongation might be underestimated. This limitation will only be minimized by performing a future prospective study where EKGs are performed on a regular base for every hospitalized COVID-19 patient.

5 | CONCLUSION

A history of ESRD, QTc ≥ 450 ms on admission, and serum potassium ≤ 3.5 mmol/L were identified in our study as significant predictors for developing QT interval prolongation in hospitalized non-ICU COVID-19 patients. Any patient who presents with these features requires preventative measures, including continuous cardiac monitoring, potassium replacement and, if possible, avoiding high-risk QT-prolonging medications.

CONFLICT OF INTEREST

Authors have no conflicts to disclose.

AUTHOR CONTRIBUTION

This study was primarily designed by W. Zhao with valuable contributions from all authors. Data were collected and interpreted by W. Zhao, N. Gandhi, and S. Affas. Statistical analysis was performed by S. Szpunar. Manuscript was drafted by W. Zhao. Manuscript was revised by L. Saravolatz, N. Mesiha, and S. Szpunar. Manuscript was approved by L. Saravolatz and N. Mesiha. W. Zhao is the corresponding author.

ETHICAL APPROVAL

This study conforms to the Declaration of Helsinki and was approved by Ascension St. John Hospital Institutional Review Board.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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